ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 1989, p. 128–130
0066-4804/89/010128-03$02.00/0

Vol. 33, No. 1

Ciprofloxacin for Methicillin-Resistant *Staphylococcus aureus* Infections

ELIZABETH A. PIERCY,[1,2]* DANIEL BARBARO,[1,2] JAMES P. LUBY,[1] AND PHILIP A. MACKOWIAK[1,2]

*Division of Infectious Diseases, University of Texas Southwestern Medical Center, Dallas, Texas 75235,[1] and Medical Service, Veterans Administration Medical Center, Dallas, Texas 75216[2]**

Received 20 June 1988/Accepted 18 October 1988

Thirty-seven patients with methicillin-resistant *Staphylococcus aureus* infections and/or colonization were treated with oral ciprofloxacin (750 mg twice a day). Clinical cure or improvement of infections occurred in 91% of the patients, and bacteriologic cure occurred in 60%. Ciprofloxacin therapy suppressed methicillin-resistant *S. aureus* colonization in 55% of the patients. Ciprofloxacin-resistant strains emerged in 6 of the 37 patients.

Infections caused by methicillin-resistant strains of *Staphylococcus aureus* (MRSA) have become an increasing problem as both community-acquired and nosocomial infections (2, 9, 10, 13, 15). The success of MRSA as a human pathogen is due, in large part, to its capacity for colonizing the human anterior nasal vestibule and other body sites and to the ease with which it is transmitted from person to person. Optimal antibiotic treatment, therefore, must eradicate colonization as well as cure infections. Vancomycin, although useful for treating most serious MRSA infections, is expensive, is not absorbed when administered orally, and has little if any effect on MRSA colonization (11, 12). Trimethoprim-sulfamethoxazole in combination with rifampin has been used successfully to eliminate the MRSA carrier state, but emergence of resistance of MRSA to trimethoprim-sulfamethoxazole and rifampin in various areas has limited the usefulness of this combination (2, 3; B. C. Brown, M. Marling Cason, and P. A. Mackowiak, unpublished results). Because ciprofloxacin has good in vitro activity against MRSA (1, 4, 5, 7, 14), we evaluated it for the treatment of MRSA infections and the MRSA carrier state in a prospective, noncomparative clinical trial.

In the investigation, we recruited patients with MRSA infections and/or colonization at the Dallas Veterans Administration Medical Center and Parkland Memorial Hospital in Dallas between December 1985 and November 1987. Patients were excluded from the study if their serum creatinine was ≥1.6 μg/ml, if they had a severe infection requiring either parenteral therapy or an antibiotic effective against MRSA, or if they had a rapidly fatal underlying disease. All patients were treated with oral ciprofloxacin (Pharmaceutical Division, Miles Laboratories, Inc., West Haven, Conn.; 750 mg every 12 h).

Antibiotic susceptibility determinations were performed by using the standard antibiotic disk technique in accordance with the modified Bauer-Kirby procedure (8). Oxacillin resistance was defined as a zone of inhibition of <10 mm around a 1-μg disk. For ciprofloxacin, organisms were considered susceptible if the zone of inhibition around a 5-μg disk was <21 mm, intermediately susceptible when the zone was 18 to 20 mm, and resistant when the zone was <18 mm. Bacterial cultures, complete blood cell counts, chemistry studies, and urinalyses were performed prior to the initiation of therapy. These were repeated on day 5 of therapy, on day 10, and at the end of therapy. Patients treated for MRSA colonization had additional cultures taken 10 to 14 and 21 to 30 days after the completion of therapy. Cultures to evaluate MRSA colonization status were taken from the nares, axilla, and groin.

Clinical responses were rated as follows: cure if there was disappearance of all signs and symptoms related to the infection, improvement if there was a marked or moderate reduction in the severity and/or number of signs and symptoms of infection, or failure if there was little or no lessening of the signs and symptoms of infection. Decubitus ulcers or postsurgical wounds were considered cured only if wound closure occurred. We defined a bacteriologic cure as the absence of MRSA at the infected site at the end of therapy, a bacteriologic relapse as the recurrence of a positive culture for MRSA following a negative culture at the end of therapy, and a bacteriologic failure as a positive culture for MRSA at the completion of therapy regardless of the clinical status of the infected site.

Plasmid isolation was carried out by a modification of the method of Kado and Liu (6). Bacteria were incubated in L broth overnight at 30°C with shaking and then pelleted by centrifugation. Following incubation in a lysostaphin solution, alkaline sodium dodecyl sulfate lysis was performed. After phenol-chloroform extraction, electrophoresis was carried out on a 0.7% agarose gel (14 by 14 cm).

Thirty-two evaluatable courses of therapy were administered for various infections (Table 1). Although only three patients were treated for infected decubitus ulcers, seven patients treated for other types of infections also had decubitus ulcers. Two subjects with osteomyelitis were treated with ciprofloxacin for 6 weeks. The remainder received ciprofloxacin for 12 to 14 days. Ciprofloxacin therapy was terminated prematurely (i.e., after <12 days) for an additional four patients because of possible adverse reactions to the drug. Ciprofloxacin was discounted on day 2 of therapy in one case because of nausea and vomiting. For another patient, with an underlying seizure disorder, ciprofloxacin therapy was terminated on day 8 of treatment because of a grand mal seizure. Serum creatinine levels increased in five patients. Ciprofloxacin was discontinued for two patients because of persistently elevated serum creatinine levels of 1.8 and 2.5 μg/ml. In three patients, creatinine levels returned to normal during therapy.

* Corresponding author.

TABLE 1. Clinical and bacteriologic responses of 32 MRSA infections to ciprofloxacin

Site of infection	No. (%) of infections with:					
	Clinical response			Bacteriologic response		
	Cure	Improvement	Failure	Cure	Failure	Secondary infection
Lung	4	2	0	4	2	0
Wound	8	7	0	11	3	1
Decubitus	0	1	2	1	2	0
Other skin structures	1	3	1	2	3	0
Bone	1	1	0	0	1	1
Urinary tract	1	0	0	1	0	0
Total	15 (47)	14 (44)	3 (9)	19 (60)	11 (34)	2 (6)

Clinical responses were judged to be cures in 15 patients (47%), improvements in 14 patients (44%), and failures in 3 patients (9%). Decubitus ulcer infections were associated with the highest failure rate (two of three patients were treatment failures). In 19 patients (60%), MRSA was eradicated from the infected site by the end of ciprofloxacin therapy. Secondary infections occurred in two patients, one with *Candida albicans* and group B streptococcus in a diabetic foot ulcer and one with *Staphylococcus epidermidis* in a sternotomy wound. In 8 of the 11 bacteriologic failures, clinical cure or improvement occurred despite the persistence of MRSA at the site of infection. Of the 21 patients with negative cultures at the end of therapy, 11 were evaluated with follow-up cultures 21 to 30 days after the completion of therapy. Bacteriologic relapses occurred in 7 of the 11 patients (64%) but were not accompanied by clinical deterioration.

Eighteen of the patients treated in the present investigation were colonized by MRSA. Thirteen had concurrent MRSA infections and were evaluated simultaneously as cases of colonization and infection. Of the 18 patients colonized by MRSA, 10 (56%) had negative cultures for MRSA at the end of therapy. However, cultures obtained 14 to 30 days after the completion of therapy showed only 17% to be free of MRSA. Gel electrophoresis patterns of plasmids from MRSA isolates obtained before and after relapses were identical for each of the three patients studied.

All pretherapy MRSA isolates were susceptible or intermediately susceptible to ciprofloxacin. In six patients, ciprofloxacin-resistant strains of MRSA emerged during therapy. For three of these patients, treatment was terminated because of an adverse reaction. Two patients exhibited clinical improvement despite bacteriologic failure of ciprofloxacin treatment, and another represented a failure in treatment for colonization.

The response rate among the subjects treated in this investigation suggests that oral ciprofloxacin might be a useful alternative to vancomycin for treating mild-to-moderately severe MRSA infections. The clinical and bacteriologic cure rates of 47 and 60%, respectively, were encouraging, particularly so because patients with infected decubitus ulcers, which were notoriously refractory to antibiotic therapy, accounted for two-thirds of the clinical failures and one-fifth of the bacteriologic failures. Nevertheless, the clinical and bacteriologic cure rates of 47 and 60%, respectively, indicate that oral ciprofloxacin is not totally efficacious against MRSA infections. Whether its efficacy is comparable to that of vancomycin for moderately severe MRSA infections is not known, since the appropriate comparative clinical trial has yet to be performed. The emergence of ciprofloxacin-resistant strains of MRSA in three of our patients during therapy raises the possibility that widespread use of ciprofloxacin or other quinolones might promote resistance of MRSA to these antibiotics in the population at large.

In a recent paper, Mulligan et al. (11) reported eradication of MRSA colonization by oral ciprofloxacin in 11 of 14 patients studied (79%). Of the 11 patients cleared of MRSA, 4 (35%) became recolonized within 1 month of completing courses of ciprofloxacin therapy varying from 7 to 28 days. In our investigation, in which patients received ≤14 days of therapy for the MRSA carrier state, ciprofloxacin was slightly less effective. The capacities of ciprofloxacin for eliminating MRSA carriage and for gastrointestinal absorption constitute potentially important advantages over vancomycin in dealing with MRSA. Unfortunately, the high rate of reemergence of MRSA colonization after therapy raised the possibility that ciprofloxacin might suppress rather than eradicate MRSA from mucosal surfaces. Since our subjects remained institutionalized throughout the period of observation, they might also have been recolonized from exogenous sources. Unfortunately, the results of plasmid profile analyses of three patients with relapsing MRSA colonization did not clarify which of these two possible explanations accounted for instances of recolonization by MRSA.

We are indebted to James Smith for advice, Justin Randolph for technical support, and Sherry Templeton for manuscript preparation.

This work was supported by the Veterans Administration and by a grant from Miles Pharmaceuticals, West Haven, Conn.

LITERATURE CITED

1. **Aldridge, K. E., A. Janney, and C. V. Sanders.** 1985. Comparison of the activities of coumermycin, ciprofloxacin, teicoplanin, and other non-β-lactam antibiotics against clinical isolates of methicillin-resistant *Staphylococcus aureus* from various geographical locations. Antimicrob. Agents Chemother. **28:** 634–638.
2. **Bacon, A. E., K. A. Jorgensen, K. H. Wilson, and C. A. Kauffman.** 1987. Emergence of nosocomial methicillin-resistant *Staphylococcus aureus* and therapy of colonized personnel during a hospital-wide outbreak. Infect. Control **8:**145–150.
3. **Bitar, C. M., C. G. Mayhall, V. A. Lamb, T. J. Bradshaw, A. C. Spadora, and H. P. Dalton.** 1987. Outbreak due to methicillin- and rifampin-resistant *Staphylococcus aureus*: epidemiology and eradication of the resistant strain from the hospital. Infect. Control **8:**15–23.
4. **Dacro, J. E., A. M. Emmerson, and E. A. Jenner.** 1983. Nasal carriage of gentamicin and methicillin-resistant *Staphylococcus aureus* treated with topical pseudomonic acid. Lancet **ii:**1036.
5. **Foster, J. K., J. R. Lentino, R. Strodtman, and C. DiVincenzo.** 1986. Comparison of in vitro activity of quinolone antibiotics and vancomycin against gentamicin- and methicillin-resistant *Staphylococcus aureus* by time-kill kinetic studies. Antimicrob.

Agents Chemother. **30**:823–827.
6. **Kado, C. I., and S. T. Liu.** 1981. Rapid procedure for detection and isolation of large and small plasmids. J. Bacteriol. **145**: 1365–1373.
7. **Kelley, S. G., M. A. Bertram, and L. S. Young.** 1986. Activity of ciprofloxacin against resistant clinical isolates. J. Antimicrob. Chemother. **17**:281–286.
8. **Lennette, E. H., A. Balows, W. J. Hausler, Jr., and J. P. Truant (ed.).** 1980. Manual of clinical microbiology, 3rd ed. American Society for Microbiology, Washington, D.C.
9. **Levine, D. P., R. D. Cushing, J. Jui, and W. J. Brown.** 1982. Community-acquired methicillin-resistant *Staphylococcus aureus* endocarditis in the Detroit Medical Center. Ann. Intern. Med. **97**:330–338.
10. **Locksley, R. M., M. L. Cohen, T. C. Quinn, L. S. Tompkins, M. B. Coyle, J. M. Kirihara, and G. W. Counts.** 1982. Multiply antibiotic-resistant *Staphylococcus aureus*: introduction, transmission, and evolution of nosocomial infection. Ann. Intern. Med. **97**:317–334.
11. **Mulligan, M. E., P. J. Ruane, L. Johnson, P. Wong, J. P. Wheelock, K. MacDonald, J. F. Reinhardt, C. C. Johnson, B. Statner, I. Blomquist, J. McCarthy, W. O'Brien, S. Gardner, L. Hammer, and D. Citron.** 1987. Ciprofloxacin for eradication of methicillin-resistant *Staphylococcus aureus* colonization. Am. J. Med. **82**(Suppl. 4A):215–219.
12. **Preheim, L. C., D. Rimland, and M. J. Bittner.** 1987. Methicillin-resistant *Staphylococcus aureus* in Veterans Administration Medical Centers. Infect. Control **8**:191–194.
13. **Saravolatz, I. D., N. Markowitz, L. Arking, D. Pohlod, and E. Fisher.** 1982. Methicillin-resistant *Staphylococcus aureus*: epidemiologic observations during a community-acquired outbreak. Ann. Intern. Med. **96**:11–16.
14. **Smith, S. M., R. H. Eng, and E. Berman.** 1986. The effect of ciprofloxacin on methicillin-resistant *Staphylococcus aureus*. J. Antimicrob. Chemother. **17**:287–295.
15. **Standiford, H. C.** 1987. Methicillin-resistant *Staphylococcus aureus* infections: it's time to get tough. Infect. Control **8**:187–189.